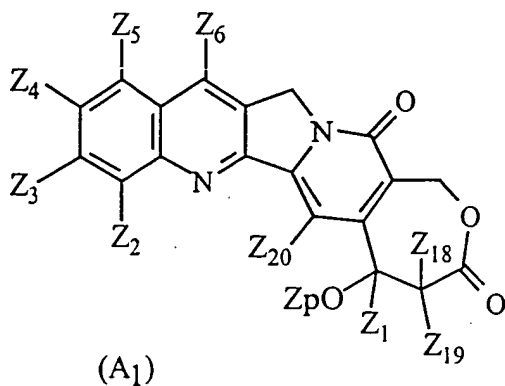
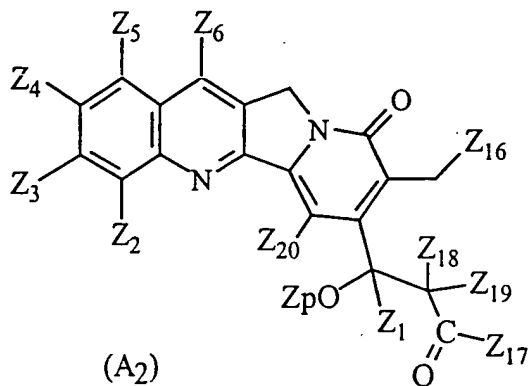


IN THE CLAIMS:

Claim 1 (amended) A compound of the formula



(A₁)



(A₂)

in racemic or enantiomeric form or any combinations of these forms,
wherein

Z₁ is a member selected from the group consisting of
lower alkyl, lower alkenyl, lower alkynyl, lower
haloalkyl, lower alkoxy lower alkyl and lower
alkylthio lower alkyl;

Z₂, Z₃, Z₄, Z₅ and Z₆ are independently a member selected from the
group consisting of,

i) H, halo, lower haloalkyl, alkyl of 1 to 12
carbon atoms unsubstituted or substituted by at
least one halo, lower alkenyl, cycloalkyl,
cycloalkyl lower alkyl, cyano, lower cyanoalkyl,

contd.
a²

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nitro, lower nitroalkyl, amido, lower amidoalkyl, hydrazino, lower hydrazinoalkyl, azido, lower azidoalkyl, lower alkyl lower sulphonylalkyl, $-(CH_2)_mNZ'_6Z'_7$, $-(CH_2)_mOZ'_6$, $-(CH_2)_mSZ'_6$, $-(CH_2)_mCO_2Z'_6$, $-(CH_2)_mCO_2Z'_6$, $-(CH_2)_mNZ'_6C(O)Z_8$, $-(CH_2)_mC(O)Z_8$, $-(CH_2)_mOC(O)Z_8$, $-O-(CH_2)_mNZ'_6Z'_7$, $-OC(O)NZ'_6Z'_7$, $-OC(O)(CH_2)_mCO_2Z'_6$, $-OSO_2Z_7$, $-(CH_2)_mN(CH_3)(CH_2)_nNZ'_6Z'_7$, $-(CH_2)_mOC(O)NZ'_6Z'_7$, $-(CH_2)_mS(O)_qZ_{11}$, $-(CH_2)_mP(O)Z_{12}Z_{13}$, $-(CH_2)_2P(S)Z_{12}Z_{13}$, $-(CH_2)_mSiZ'_{11}Z'_{12}Z'_{13}$; or ii) $-(CH_2)_n[N=X]$, $-OC(O)[N=X]$, $-(CH_2)_mOC(O)[N=X]$, aryl and lower arylalkyl, each unsubstituted or substituted with 1 to 4 members on the aryl or the heterocycle selected from the group consisting of lower alkyl, lower arylalkyl, halo, hydroxy, $-OCF_3$, nitro, amino, lower alkylamino, di(lower alkyl)amino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl or iii) Z_3 and Z_4 or Z_4 and Z_5 form together a chain of 3 or 4 members in which the elements of the chain are selected from the group consisting of CH, CH_2 , O, S, N or NZ_9 ;

Z_7

is a member selected from the group consisting of lower alkyl unsubstituted or substituted by at least one halo, aryl, aryl unsubstituted or substituted by at least one lower alkyl;

contd.
a²

Z', and Z',

are independently a member selected from the group consisting of i) H, lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl and haloalkyl, or ii) aryl or lower arylalkyl, unsubstituted or substituted on the aryl with 1 to 4 members selected from the group consisting of lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl;

Z₈

is a member selected from the group consisting of i) H, lower alkyl, lower hydroxyalkyl, amino, lower alkylamino, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy, lower alkoxy lower alkyl and lower haloalkyl, or ii) aryl or lower arylalkyl unsubstituted or substituted on the aryl with 1 to 4 members selected from the group consisting of lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl;

Z₉

is a member selected from the group consisting of

contd.

Q 2

i) H, lower alkyl, lower haloalkyl, or ii) aryl and lower arylalkyl unsubstituted or substituted with a member selected from the group consisting of lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxalkyl, lower alkoxy and lower alkoxy lower alkyl;

Z₁₀

is a member selected from the group consisting of i) H, lower alkyl, lower haloalkyl and lower alkoxy, or ii) aryl unsubstituted or substituted on the aryl with a member selected from the group consisting of lower alkyl, lower haloalkyl, lower hydroxyalkyl and lower alkoxy lower alkyl;

Z₁₁

is a member selected from the group consisting of lower alkyl, aryl, $-(CH_2)_mOZ_{14}$, $-(CH_2)_mSZ_{14}$, $-(CH_2)_2NZ_{14}Z_{15}$ and $(CH_2)_m[N=X]$;

Z₁₂ and Z₁₃

are independently members selected from the group consisting of lower alkyl, aryl, lower alkoxy, aryloxy and amino;

Z'₁₁, Z'₁₂ and

Z'₁₃

are independently a member selected from the group consisting of H or lower alkyl;

Z₁₄ and Z₁₅

are independently a member selected from the group

contd.
a²

consisting of H, lower alkyl and aryl;

Z₁₆

is H or -OZ₂₁;

Z₁₇

is -OZ'₆ or -NZ'₆ or -NZ'₆Z'₇;

Z₁₈ and Z₁₉

are independently a member selected from the group consisting of H, halo, lower alkyl, lower alkoxy and hydroxy;

Z₂₀

is H or halo;

Z₂₁

is a member selected from the group consisting of H, lower alkyl, -CHO and -C(O)(CH₂)_mCH₃;

Z_p

is a member selected from the group consisting of H or an easily cleavable group preferably chosen from the groups corresponding to the formula -C(O)-A-NZ₂₂Z₂₃, in which A represents a linear or branched alkylene unsubstituted or substituted by a member selected from the group consisting of free, esterified or salified hydroxy, halogen, free, esterified or salified carboxy, amino, mono and dialkylamino;

contd.
a²

Z_{22} and Z_{23}

are independently a member selected from the group consisting of i) H, lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl, lower haloalkyl, or ii) aryl or lower arylalkyl unsubstituted or substituted on the aryl with 1 to 4 members selected from the group consisting of lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl;

m

is an integer between 0 and 6;

n

is 1 or 2; and

q

is an integer from 0 to 2; and

[N=X]

is a heterocyclic group with 4 to 7 ring members with the nitrogen atom which a member of the heterocyclic ring, and X is the chain necessary to complete said heterocyclic group and selected from the group consisting of O, S, CH_2 , CH, N, NZ_9 , and $C(O)Z_{10}$;

and its pharmaceutically acceptable salt.

contd.
a²

Claim 2 (amended) A compound of claim 1, in racemic or enantiomeric form or any combinations of these forms, wherein

Z₁ is a member selected from the group consisting of lower alkyl, lower alkenyl, lower alkynyl, lower haloalkyl, lower alkoxy lower alkyl and lower alkylthio lower alkyl;

Z₂ is a member selected from the group consisting of H, halo and -OSO₂Z₇;

Z₃, Z₄ and Z₅ are independently a member selected from the group consisting of i) H, halo, lower haloalkyl, lower alkyl, lower alkenyl, cyano, lower cyanoalkyl, nitro, lower nitroalkyl, amido, lower amidoalkyl, hydrazino, lower hydrazinoalkyl, azido, lower azidoalkyl, -(CH₂)_mNZ'₆Z'₇, -(CH₂)_mOZ'₆, -(CH₂)_mSZ'₆, -(CH₂)_mCO₂Z'₆, -(CH₂)_mNZ'₆C(O)Z₈, -(CH₂)_mC(O)Z₈, -(CH₂)_mOC(O)Z₈, -O(CH₂)_mNZ'₆Z'₇, -OC(O)NZ'₆Z'₇, -OC(O)(CH₂)_mCO₂Z'₆ and -OSO₂Z₇ or ii) -(CH₂)_n[N=X], -OC(O)[N=X], -(CH₂)_mOC(O)[N=X] wherein [N=X] is a heterocyclic group with 4 to 7 ring members with the nitrogen atom, which is a member of the heterocyclic group, and X is the remaining members, which are necessary to complete the heterocyclic group, selected from the group consisting of O, S,

contd.
a2

CH₂, CH, N, NZ₉ and COZ₁₀, aryl or lower arylalkyl, unsubstituted or substituted on the aryl or the heterocycle with 1 to 4 members selected from the group consisting of lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl or iii) Z₃ and Z₄ or Z₄ and Z₅ form together a chain with 3 or 4 members in which the elements of the chain are selected from the group consisting of CH, CH₂, O, S, N and NZ₉;

Z₆

is a member selected from the group consisting of i) H, halo, lower haloalkyl, alkyl containing 1 to 12 carbon atoms unsubstituted or substituted by at least one halo, lower alkoxy, lower alkoxy lower alkyl, lower alkylthio lower alkyl, cycloalkyl, cycloalkyl lower alkyl, cyano, cyanoalkyl, lower alkyl lower sulphonylalkyl, lower hydroxyalkyl, nitro, $-(CH_2)_mC(O)Z_8$, $-(CH_2)_mNZ'_6C(O)Z_8$, $-(CH_2)_mNZ'_6Z'_7$, $-(CH_2)_mN(CH_3)(CH_2)_nNZ'_6Z'_7$, $-(CH_2)_mOC(O)Z_8$, $-(CH_2)_mOC(O)NZ'_6Z'_7$, $-(CH_2)_mS(O)_qZ_{11}$, $-(CH_2)_mP(O)Z_{12}Z_{13}$, $-(CH_2)_2P(S)Z_{12}Z_{13}$, and $-(CH_2)_mSiZ'_{11}Z'_{12}Z'_{13}$; or ii) $-(CH_2)_n[N=X]$, $-OC(O)[N=X]$, $-(CH_2)_mOC(O)[N=X]$, each unsubstituted or unsubstituted on the heteroaryl with 1 to 4 members of the group consisting of lower alkyl, lower

contd.
a²

arylalkyl, halo, hydroxy, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl; or iii) aryl or lower arylalkyl, each unsubstituted or substituted on the aryl with 1 to 4 members of the group consisting of lower alkyl, halo, hydroxy, nitro, -OCF₃, amino, lower alkylamino, di(lower alkyl)amino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl;

Z₇

is a member selected from the group consisting of lower alkyl unsubstituted or substituted by at least one halo, or unsubstituted or substituted by at least one lower alkyl;

Z'₆ and Z'₇

are independently a member selected from the group consisting of i) H, lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl and lower haloalkyl, or ii) aryl or lower arylalkyl unsubstituted or substituted on the aryl with 1 to 4 members of the group consisting of lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl;

contd.
A²

Z₈

is a member selected from the group consisting of
i) H, lower alkyl, lower hydroxyalkyl, amino, lower
alkylamino, lower alkyl lower aminoalkyl, lower
aminoalkyl cycloalkyl, cycloalkyl lower alkyl,
lower alkenyl, lower alkoxy, lower alkoxy lower
alkyl and lower haloalkyl, or ii) aryl or lower
arylalkyl unsubstituted or substituted on the aryl
with 1 to 4 members of the group consisting of
lower alkyl, halo, nitro, amino, lower alkylamino,
lower haloalkyl, lower hydroxyalkyl, lower alkoxy
and lower alkoxy lower alkyl;

Z₉

is a member selected from the group consisting of
i) H, lower alkyl and lower haloalkyl, or ii) aryl
or lower arylalkyl unsubstituted or substituted
with a member of the group consisting of lower
alkyl, halo, nitro, amino, lower alkylamino, lower
haloalkyl, lower hydroxyalkyl, lower alkoxy and
lower alkoxy lower alkyl;

Z₁₀

is a member selected from the group consisting of
i) H, lower alkyl, lower haloalkyl and lower
alkoxy, or ii) aryl unsubstituted or substituted on
the aryl with 1 to 4 members of the group
consisting of lower alkyl, lower haloalkyl, lower
hydroxyalkyl and lower alkoxy lower alkyl;

contd.
a²

Z_{11} is a member selected from the group consisting of lower alkyl, aryl, $-(CH_2)_mOZ_{14}$, $-(CH_2)_mSZ_{14}$, $-(CH_2)_2NZ_{14}Z_{15}$ and $-(CH_2)_m[N=X]$;

Z_{12} and Z_{13} are independently a member selected from the group consisting of lower alkyl, aryl, lower alkoxy, aryloxy and amino;

Z'_{11} , Z'_{12} and Z'_{13} are independently H or lower alkyl;

Z_{14} and Z_{15} are independently a member selected from the group consisting of H, lower alkyl and aryl;

Z_{16} is H or $-OZ_{21}$;

Z_{17} is OZ'_6 or $-NZ'_6Z'_7$;

Z_{18} and Z_{19} are independently a member selected from the group consisting of H, halo, lower alkyl, lower alkoxy and hydroxy;

Z_{20} is H or halo;

Z_{21} is a member selected from the group consisting of H, lower alkyl, $-CHO$ and $-C(O)(CH_2)_mCH_3$;

contd.
a²

Z_p

represents H or an easily cleavable group of the formula $-C(O)-A-NZ_{22}Z_{23}$, wherein A is alkylene unsubstituted or substituted by a member selected from the group consisting of free, esterified or salified hydroxy, halogen, free, esterified or salified carboxy, amino and mono and dialkylamino;

Z_{22} and Z_{23}

are independently a member selected from the group consisting of i) H, lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl, lower haloalkyl, or ii) aryl or lower arylalkyl unsubstituted or substituted by 1 to 4 members of the group consisting of lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy and lower alkoxy lower alkyl;

m

is an integer between 0 and 6; and

n

is 1 or 2; and

q

is an integer from 0 to 2; and

[N=X]

is a heterocyclic group with 4 to 7 ring members

contd.
a²

with the nitrogen atom which is a member of the heterocyclic ring, and X is the chain necessary to complete said heterocyclic group and is selected from the group consisting of O, S, CH₂, CH, N, NZ, and COZ₁₀;

and a pharmaceutically acceptable salt thereof.

Claim 3 (amended) A compound of claim 1 wherein Z₂ is H or halo and pharmaceutically acceptable salt thereof.

Claim 4 (amended) A compound of claim 1 wherein Z₃ is halo; and a pharmaceutically acceptable salt thereof.

Claim 5 (amended) A compound of claim 1 wherein

Z₁ is lower alkyl;

Z₂ is H or halo;

Z₃, Z₄ and Z₅ are independently a member selected from the group consisting of i) H, halo, lower alkyl, -(CH₂)_mNZ'₆Z'₇, -(CH₂)_mOZ'₆ and -OSO₂Z₇ or ii) -(CH₂)_n[N=X] or iii) Z₃ and Z₄ or Z₄ and Z₅ form together a chain with 3 or 4 members in which the elements of the chain are selected from the group

contd.
a²

consisting of CH, CH₂, O, S, N and NZ₉;

Z₆ is a member selected from the group consisting of
i) H, halo, alkyl of 1 to 12 carbon atoms
unsubstituted or substituted by at least one halo,
lower alkoxy lower alkyl, cycloalkyl, cycloalkyl
lower alkyl, lower hydroxyalkyl, -(CH₂)_mNZ'₆Z'₇ and
-(CH₂)_mSiZ'₁₁Z'₁₂Z'₁₃; or ii) -(CH₂)_n[N=X] unsubstituted
or substituted with lower alkyl or lower arylalkyl
or iii) aryl or lower arylalkyl unsubstituted or
substituted with a member selected from the group
consisting of lower alkyl, halo, -OCF₃, di(lower
alkyl)amino and lower haloalkyl;

Z₇ is lower alkyl unsubstituted or substituted by at
least one halo;

Z'₆ and Z'₇ are independently i) H, or lower alkyl, or ii)
lower arylalkyl;

Z₉ is lower alkyl or lower arylalkyl;

Z'₁₁, Z'₁₂ and Z'₁₃ are independently lower alkyl;

Z₁₆ is H or -OZ₂₁;

contd.
a 2

Z_{17} is $-OZ'_6$ or $-NZ'_6Z'_7$;

Z_{18} and Z_{19} are independently H or halo;

Z_{20} is H;

Z_{21} is a member selected from the group consisting of H, lower alkyl or $-C(O)(CH_2)_mCH_3$;

Z_p is H or $-C(O)-A-N_{22}Z_{23}$, in which A is alkylene unsubstituted or substituted by a member selected from the group consisting of free, esterified or salified hydroxy, halogen, free, esterified or salified carboxy, amino and mono and dialkylamino radicals;

Z_{22} and Z_{23} are independently H or lower alkyl;

m is an integer between 0 and 6;

n is 1 or 2; and

q is an integer from 0 to 2; and

[N=X] is a heterocyclic group with 4 to 7 ring members, X is the chain necessary to complete said

contd.
a²

heterocyclic group and is selected from the group consisting of O, CH₂, CH, N and NZ₉;

and a pharmaceutically acceptable salt thereof.

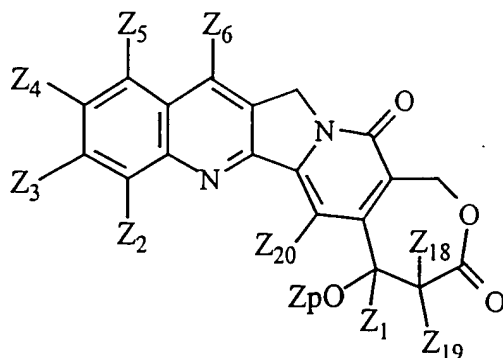
Claim 6 (amended) A compound of claim 1 wherein Z₁₈, Z₁₉ and Z₂₀ are H; and a pharmaceutically acceptable salt thereof.

Claim 7 (amended) A compound of claim 1 wherein Z₁ is ethyl and a pharmaceutically acceptable salt thereof.

Claim 8 (amended) A compound of claim 1 wherein Z_p is -C(O)-A-NZ₂₂Z₂₃ and a pharmaceutically acceptable salt thereof.

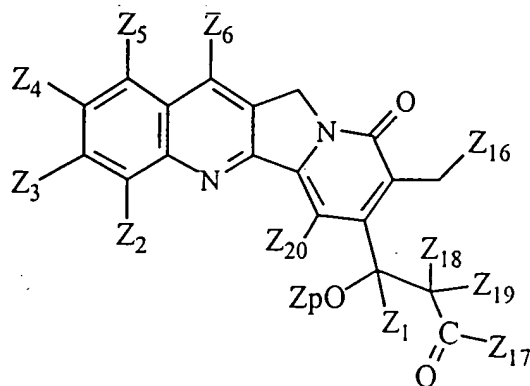
Claim 9 (amended) A compound of claim 1 wherein Z_p is H and a pharmaceutically acceptable salt thereof.

Claim 10 (amended) A compound of claim 1 having the formula



contd.
a² wherein Z₁, Z₂, Z₃, Z₄, Z₅, Z₆, Z₁₈, Z₁₉, Z₂₀ and Z_p are as defined in claim 1 and a pharmaceutically acceptable salt thereof.

Claim 11 (amended) A compound of claim 1 having the formula



wherein Z₁, Z₂, Z₃, Z₄, Z₅, Z₆, Z₁₆, Z₁₇, Z₁₈, Z₁₉, Z₂₀ and Z_p are as defined in claim 1 and a pharmaceutically acceptable salt thereof.

Claim 12 (amended) A compound of claim 1 wherein Z₆ is $-(CH_2)_mSiZ'_{11}Z'_{12}Z'_{13}$ and a pharmaceutically acceptable salt thereof.

Claim 13 (amended) A compound of claim 1 selected from the group consisting of:

(5R)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1H,3H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione; and

(5R)-5-ethyl-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-

contd.
a²

tetrahydro-1H,3H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione.

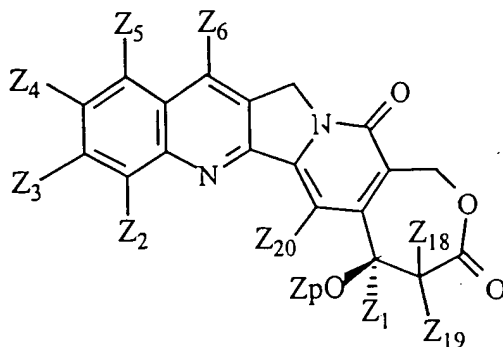
Claim 14 (amended) A compound of claim 1 wherein Z₂ is H or halo, Z₃ is halo, Z₄ is a member selected from the group consisting of H, halo and lower alkyl, Z₅ is H or halo, and Z₆ is a member selected from the group consisting of H, lower alkyl and -(CH₂)_n[N=X] substituted with lower alkyl and a pharmaceutically acceptable salt thereof.

Claim 15 (amended) A compound of claim 1 selected from the group consisting of:

(5R)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1H,3H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione; and

(5R)-5-ethyl-9,11-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1H,3H-oxepino[3,4':6,7]indolizino[1,2-b]quinoline-3,15-dione; and a pharmaceutically acceptable salt thereof.

Claim 16 (amended) A compound of claim 1 having the formula



contd.
a² wherein $Z_1, Z_2, Z_3, Z_4, Z_5, Z_6, Z_{18}, Z_{19}, Z_{20}$ and Z_p are as defined in claim 1 and a pharmaceutically acceptable salt thereof.

a³ Claim 22 (amended) A method of treating cancer as claimed in claim 17, wherein the cancer is selected from the group consisting of leukemia, colon cancer, lung cancer, prostate cancer, breast cancer, melanoma, ovarian cancer and gastric cancer.

Claim 23 (amended) A method of treating cancer as claimed in claim 22, wherein the cancer is selected from the group consisting of leukemia, colon cancer, lung cancer, prostate cancer and breast cancer.

Claim 24 (amended) A method of claim 17 wherein R_{18} and R_{19} are hydrogen.

Claim 25 (amended) A method of claim 17 wherein R_p is hydrogen.

Claim 26 (amended) A method of claim 17 wherein R_i is ethyl.

Claim 27 (amended) A method of claim 17 wherein the camptothecin analog is selected from the group consisting of:

(5R)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1H,3H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione;